

AMENDMENTS TO THE SPECIFICATION

At page 1, replace lines 3 to 5 with the following:

This application is a Divisional of and claims priority to U.S. patent application Ser. No. 09/919,243 filed Jul. 31, 2001, now ~~pending~~ abandoned and expressly incorporated by reference herein in its entirety.

Replace the paragraph beginning at page 4, line 14 with the following amended paragraph:

The composition and use of internal image antibody conjugates to achieve specificity for photodiagnostic and phototherapeutic applications, without the need to isolate a particular receptor, are disclosed. The invention discloses novel bioconjugates of internal image anti-idiotypic antibodies, or antibody fragments which contain the desired epitope for binding (hereinafter referred to as antibody fragment), that are attached to photoactive molecules (PM) for photodiagnostic or phototherapeutic purposes. These are generally represented by the following structure:

Ab - PM

where Ab is a whole internal image antibody or antibody fragment directed to a particular biological receptor and PM is a photoactive molecule such as dyes, photosensitizers or precursors for producing reactive intermediates. The internal image antibody is directed to a biological receptor, for example, receptors for steroids, cardiac glycosides, somatostatin, bombesin, cholecystokinin (CCK), neurotensin, or ~~heat sensitive bacterioendotoxin (ST)~~ heat stable toxin. In some embodiments, a linker may link Ab and PM, represented as Ab-L-PM. The linker may be -HNCONH-, -HNCSNH-, -HNCO-, -CONH-, -S(CH₂)_mCONH-, or -S-(N-succinimido)-(CH₂)_nCONH-, with m and n varying from 1 to 10.

Replace the paragraph beginning at page 6, line 12 with the following amended paragraph:

The invention also discloses a method for performing a diagnostic procedure using internal image antibody bioconjugates. In the method, a ligand is selected that binds to a biological receptor, such as the receptor for steroids, cardiac glycosides, somatostatin, bombesin, cholecystokinin, neurotensin, and ~~heat sensitive bacterioendotoxin (ST)~~ heat stable toxin. The receptor-binding ligand may be one or more drugs, hormones, peptides, carbohydrates, nucleosides, peptidomimetics, glycomimetics, or biosynthetic intermediates. The ligand used as the first generation antigen may be the complete ligand, or may be a certain region of the ligand such a fragment that binds the receptor with high affinity, etc. The receptor-binding ligand is prepared as a first generation antigen, optionally conjugating the receptor-binding ligand to an immunogenic carrier. The immunogenic carrier may be, for example, bovine serum albumin, rabbit serum albumin, or human serum albumin.

Replace the paragraph beginning at page 12, line 7 with the following amended paragraph:

The inventive diagnostic compositions comprise anti-receptor internal image antibody conjugates of formula 1,



wherein Ab is a whole or fragmented internal image antibody which retain binding affinities directed at a particular biological receptor. The internal image antibodies of the invention are directed at receptors for steroids, cardiac glycosides (e.g., digoxin), somatostatin, bombesin, neurotensin, cholecystokinin (CCK) and ~~heat-sensitive bacterioendotoxin-(ST)~~ heat stable toxin, (see, for example, U.S. Patent No. 5,518,888, which is expressly incorporated by reference herein in its entirety). In some embodiments, a linker (L) links Ab and Dye, represented as Ab-L-Dye. The linker may be -HNCONH-, -HNCSNH-, -HNCO-, -CONH-, -S(CH₂)_mCONH-, and -S-(N-succinimido)-(CH₂)_nCONH-, where m and n vary from 1 to 10. The dye is a fluorophore or a chromophore capable of absorbing or emitting light having a wavelength in the range of 300-1200 nm.

Replace the paragraph beginning at page 13, line 7 with the following amended paragraph:

In another particular embodiment of a diagnostic conjugate, Ab is directed at a receptor for steroids, bombesin, neurotensin, or ~~heat-sensitive bacterioendotoxin-(ST)~~ heat stable toxin; L is a linker and may be -HNCONH-, -HNCO-, or -S-(N-succinimido)-(CH₂)_nCONH- and n varies from 1 to 6; and the dye is an aromatic or a heteroaromatic radical derived from a cyanine, an indocyanine, a rhodamine, a phenothiazine, a fluorescein, or an azo compound.

Replace the paragraph beginning at page 13, line 12 with the following amended paragraph:

The inventive therapeutic compositions comprise anti-receptor internal image antibody conjugates of formula 2,



wherein Ab is a whole or fragmented internal image antibody directed at a particular biological receptor. The internal image antibodies of the invention are directed at receptors for steroids, cardiac glycosides (e.g., digoxin), somatostatin, bombesin, cholecystokinin, neurotensin, or ~~heat-sensitive bacterioendotoxin-(ST)~~ heat stable toxin. A linker L may link Ab and PS or PS-Q, represented as Ab-L-PS(-Q), and L may be -HNCONH-, -HNCSNH-, -HNCO-, -CONH-, -S(CH₂)_mCONH-, or -S-(N-succinimido)-(CH₂)_nCONH-, where m and n vary from 1 to 10. PS is a photosensitizing aromatic or a heteroaromatic radical derived from a benzene, a polyfluorobenzene, a naphthalene, a naphthoquinone, an anthracene, an anthraquinone, a phenanthrene, a tetracene, a naphthacenedione, a pyridine, a quinoline, an isoquinoline, an indole, an isoindole, a pyrrole, an imidazole, a pyrazole, a pyrazine, a purine, a

benzimidazole, a benzofuran, a dibenzofuran, a carbazole, an acridine, an acridone, a phenanthridine, a thiophene, a benzothiophene, a dibenzothiophene, a xanthene, a xanthone, a flavone, a coumarin, or an anthracylene. Q is either a precursor for producing reactive intermediates such as free radicals, nitrenes, carbenes, and the like, and may be an azide ($-N_3$), a cyclic azo compound ($-N=N-$), or a sulfenate ($-O-S-$).

Replace the paragraph beginning at page 14, line 8 with the following amended paragraph

In one particular embodiment of a therapeutic conjugate, the conjugates have the general formula



wherein Ab is directed at a receptor for steroids, bombesin, neurotensin, or heat-sensitive ~~bacterioendotoxin (ST)~~ heat stable toxin; L is a linker of $-HNCONH-$, $-HNCSNH-$, $-HNCO-$, or $-S-(N-succinimido)-(CH_2)_nCONH-$ and n varies from 1-6; PS is a benzene, a polyfluorobenzene, an anthracene, an anthraquinone, a naphthacenedione, a quinoline, an isoquinoline, an indole, an acridine, an acridone, a phenanthridine, a xanthene, a xanthone, or an anthracylene; and Q is an azide ($-N_3$) or a sulfenate ($-O-S-$).

Replace the paragraph beginning at page 14, line 19 with the following amended paragraph:

In another particular embodiment of a therapeutic conjugate, the conjugates have the general formula



wherein Ab is directed at a receptor for steroids, bombesin, neurotensin, or heat-sensitive ~~bacterioendotoxin (ST)~~ heat stable toxin; L is a linker of $-HNCONH-$, $-HNCO-$, or $-S-(N-succinimido)-(CH_2)_nCONH-$ and n varies from 1 to 6; PS is a tetrafluorobenzene, a phenanthridine, a xanthone, an anthraquinone, an acridine, or an acridone; and Q is an azide ($-N_3$).